IN THE U.S. PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Appeal No.
Paolo MORAZZONI et al.	Conf. 5191
Application No. 10/587,468	Group 1655
Filed November 27, 2006	Examiner Qiuwen Mi

USE OF A GINKGO COMPLEXES FOR THE ENHANCEMENT OF COGNITIVE FUNCTIONS AND THE ALLEVIATION OF MENTAL FATIGUE

APPEAL BRIEF

MAY IT PLEASE YOUR HONORS:

(1) Real Party in Interest

The real parties in interest in this appeal are the inventors, Paolo MORAZZONI, Orlando PETRINI, Andrew SCHOLEY and David KENNEDY.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 1-22 have been canceled. Claims 23-46 are pending in this application. Claims 43-45 are withdrawn. Claims 23-42 and 46 are rejected, from whose final rejection this appeal is taken.

(4) Status of Amendments

A Final Office Action was mailed on December 3, 2009.

No Amendments have been filed subsequent to the final rejection.

(5) Summary of Claimed Subject Matter

The claimed subject matter is directed to methods for enhancing cognitive function and alleviating mental fatigue in a subject comprising administering Ginkgo complexed with phospholipid. The phosholipid comprises 10-50% phosphatidylserine. The methods can improve memory speed and memory quality and counteract cognitive fatigue in normal healthy persons, or prevent deterioration of memory speed in people with decreased cognitive functions. The claimed subject matter is also directed to methods for treating diseases related to reduced cognitive function and mental fatigue such as dementia and Alzheimer's disease. (specification, Abstract, page 3, lines 16-26, page 4, lines 1-5, and page 5, lines 10-13).

Ginkgo is believed to have nootropic properties and has been used as a memory and concentration enhancer. Extracts of *Ginkgo* leaves contain flavonoid glycosides and terpenoids and the active components of Ginkgo are alkylated phenols such as ginkgol and 3-(8-pentadecenyl) phenol, and phenolic carboxylic acids such as 2-hydroxy-6-(8-pentadecenyl) benzoic acid, ginkgolide and bilobalide (page 1, lines 12-18).

There have been a variety of studies on the influence of *Ginkgo biloba* extract on cognitive performance (page 2, lines 15-24). The effects according the presently claimed methods, however, are superior to those previously described in the art.

The present inventors determined that a *Ginkgo biloba* extract complexed with phosphatidylserine can significantly enhance cognitive function and reduce mental fatigue to a greater extent than that provided by a combination of non-complexed phospholipid and ginkgo extract. The production of the complex provides new structures with ginkgo extracts which retain the unaltered structure of the compound but exhibit a several-fold increase in specific activity (page 9, lines 14-21).

The present invention refers to the use of Ginkgo complexed with phosphatidylserine (Ginkgo-PS). The Ginkgo-PS complex is obtained from a reaction of the active ingredients of an extract of ginkgo with a phospholipid containing phosphatidylserine (page 6, lines 14-21, page 9, lines 10-13). The resulting complex exhibits a greater activity as compared to Ginkgo in free form and is suitable for incorporation in most common pharmaceutical formulations (page 9, lines 2-4).

(6) Grounds of Rejection to be Reviewed on Appeal

The issue for review is whether claims 23-42 and 46 were properly rejected under 35 U.S.C. § 103(a) as being unpatentable over SUMMERS (US 6,733,797), in view of LOEW (Wiener medizinische Wochenschrift (1946), (2002) Vol. 152, No. 15-16, pp. 418-22, Ref: 40), and further in view of CARINI et al. (Planta Med 67 (2001) 326-330).

(7) Arguments

Present claim 23 is directed to a method for the enhancement of cognitive function and alleviation of mental fatigue comprising administering Ginkgo complexed with phospholipid containing phosphatidylserine. Claims 24-34 and 46 depend from claim 23 and stand together with claim 23.

Present claim 35 is directed to a method for the enhancement of cognitive function and alleviation of mental fatigue by improving the speed of memory and memory quality, by counteracting cognitive fatigue in normal healthy persons or by preventing deterioration of the speed of memory in people with decreased cognitive function, comprising administering Ginkgo complexed with phosphatidylserine. Claim 35 stands alone.

Present claim 36 is directed to a method for the treatment and prevention of a disease related with the reduction of cognitive function and mental fatigue, comprising administering Ginkgo complexed with phosphatidylserine. Claims 37-42 depend from claim 36 and stand together with claim 36.

A. Claims 23-34 and 46

The references fail to teach or suggest a ginkgo-phospholipid complex containing phosphatidylserine to enhance cognitive function and alleviate mental fatigue.

SUMMERS teaches a supplement combination that includes a phosphoester and an antioxidant (SUMMERS, column 3, lines 59-64). The phosphoester can include phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine and phosphatidylinositol (column 4, lines 9-13). The antioxidant can include any member selected from a large list of herbal, amino acid, mineral and vitamin antioxidants, one of which is listed as *ginkgo biloba* (column 4, lines 14-32).

LOEW describes additional details regarding the components of a Ginkgo extract.

SUMMERS discloses that the supplement combination is "found to give improved nervous system function with improved cognitive function and mental energy" (column 6, 50-53), and that the combination exhibits "synergistic antioxidant and restorative effects on the nervous system effective in treating neurodegenerative disorders where oxidative injury is believed to be contributory" (column 6, 54-57).

Present claim 23 is directed to a method for the enhancement of cognitive function and alleviation of mental fatigue comprising administering Ginkgo complexed with phospholipid containing phosphatidylserine. The Office Action

recognizes that SUMMERS and LOEW fail to teach or suggest Ginkgo complexed with phospholipid (see December 3, 2009 Office Action, page 4, first full paragraph) and that SUMMERS and LOEW fail to teach or suggest any method of using such Ginkgo-phospholipid complexes for the enhancement of cognitive function and the alleviation of mental fatigue as presently claimed (see, June 26, 2009 Office Action, page 5, last paragraph). For these important features, the Office Action relies on CARINI.

The Office Action relies on CARINI for teaching that a Ginkgo-phosphatidylcholine complex has cardioprotective activity and increases plasma antioxidant capacity, but then extends this teaching to ginkgo-phosphatidylserine complexes and for improving neuron function.

CARINI compares in rat the cardio-protective efficacy and the total plasma antioxidant activity of a standardized Ginkgo extract complexed with phophatidylcholine. CARINI is limited to studies in rats demonstrating complexation of Ginkgo with phosphtidylcholine, and to studies showing that after a short treatment a greater resistance of the heart to ischemia/reperfusion damage perhaps due to increased plasma antioxidant activity.

First, CARINI fails to teach or suggest the complexation of Ginkgo with any other specific phospholipids other than phosphatidylcholine. CARINI also fails to disclose to one of ordinary skill in the art any reason to select another

phospholipid among the many existing possibilities, and in particular, phosphatidylserine instead of phosphatidylcholine, and then to complex the phospholipid with *ginkgo biloba* extract.

CARINI, like SUMMERS and LOEW, fails to teach or suggest a Ginkgo-phosphatidylserine complex such as that described in the instant specification, and as featured in the instant claims. Specifically, all three references fail to recognize that a *Ginkgo biloba* extract complexed with phosphatidylserine has significant effects above a non-complexed Ginkgo extract.

As indicated at page 6, lines 22-28, and at page 7, lines 1-4 of the present specification, "Ginkgo shows a strong affinity for phospholipids, resulting in the generation of bonds which markedly modify the physiochemical and spectroscopic characteristics of the new molecules . . . Therefore, the formation of Ginkgo phospholipids complexes enables the preparation of new biologically active compositions. In fact, they possess physico-chemical and spectroscopic characteristics which are markedly different from those of the original components and as such they can be incorporated as active principle into pharmaceutical formulations."

Because the complexation between Ginkgo and phospholipids modifies the physiochemical and spectroscopic characteristics with respect to the starting (parent) compounds, the different relevant therapeutic activity associated with the different corresponding derived complexes obtainable by

complexation of Ginkgo with the many available different phospholipids was not foreseeable.

One of ordinary skill in the art, in view of the teachings of SUMMER, LOEW and CARINI, would have no reason to select phosphatidylserine in order to achieve the desired therapeutic purpose - the enhancement of cognitive function and alleviation of mental fatigue. As described in the specification, applicants have unexpectedly found that a *Ginkgo biloba* extract complexed with phosphatidylserine can be used to enhance cognitive function and alleviate mental fatigue significantly above the levels provided not only by the non-complexed extract but also by the extract complexed with phosphotidylcholine. Indeed, applicants have demonstrated that a Ginkgo-phosphatidylserine complex provides superior results in cognitive function when compared to the Ginkgo-phosphatidylcholine complex disclosed in CARINI (page 22, lines 15-28; Figs. 1-6).

Furthermore, CARINI fails to teach or suggest anything that Ginkgo complexed with any phosholipid of phosphoester could be used in a possible method for the enhancement of cognitive function and alleviation of mental fatigue. CARINI merely mentions, in the Introduction, the possible use of *Ginkgo biloba* for treating cerebral ischemia. Even in this limited suggested use of Ginkgo, CARINI fails to demonstrate any experimental data in this regard. Indeed, CARINI fails to teach or suggest anything that the plasma antioxidant activity of Ginkgo-

phosphatidylcholine complex may be somewhat useful in the brain, or in particular, the enhancement of cognitive function and alleviation of mental fatigue as presently claimed.

The presently claimed method enhances cognitive function and alleviates mental fatigue, i.e., it improves the factors related therewith such as the speed of memory and memory quality, increases accuracy and attention in activities in normal and healthy subjects, prevents deterioration of the speed and quality of memory in people with decreased cognitive functions, counteracts cognitive fatigue, and influences the mood (page 4, lines 6-13). In cognitive assessment tests and results, *Ginkgo biloba* extract complexed with phosphatidylserine has outstanding efficacy compared with other tested species, i.e., non-complexed *Ginkgo* or *Ginkgo*-phosphatidylcholine complex, in Quality of Memory, Picture Recognition Accuracy, Speed of Memory, Timed Memory Tasks, and other tasks concerning attention (*see* page 16, line 16 to page 29, line 5, and Figures 1-6).

Further support for the unexpectedly superior results of a *Ginkgo*-phosphatidylserine complex was provided in the Rule 132 Declaration of Ezio Bombardelli, submitted with the Amendment dated May 29, 2009. The Declaration includes the results of experiments carried out on 15 subjects, each subject treated with capsules respectively containing: *Ginkgo biloba* extract (GBE); phospholipids containing 20% phosphatidylserine (PS); mechanical mixtures containing *Ginkgo biloba* extract and phosphatidylserine

(GBE + PS); and *Ginkgo*-phosphatidylserine complexes (Complex). Speed of Memory, Quality of Memory, and Picture Recognition Accuracy were evaluated as disclosed in the specification. The results demonstrate that capsules containing *Ginkgo*-phosphatidylserine complex show a remarkably higher and statistically meaningful activity than that of capsules filled with *Ginkgo biloba* extract, phosphatidylserine, or mixtures of *Ginkgo biloba* extract and phosphatidylserine. The results of Speed of Memory tests are shown in the graph in the Declaration.

For all of the reasons set forth above, SUMMER, LOEW and CARINI fail to teach or suggest, and fail to render obvious, a method for enhancing cognitive function and alleviating mental fatigue comprising administering Ginkgo complexed with phospholipid containing phosphatidylserine. Accordingly, this aspect of the rejection cannot be maintained.

B. Claim 35

The references fail to teach or suggest a ginkgo-phosphatidylserine complex to improve the speed of memory and memory quality, counteracting cognitive fatigue in normal healthy persons or preventing deterioration of the speed of memory in people with decreased cognitive function.

As detailed in the above remarks, SUMMERS discloses a supplement combination of a phosphoester and an antioxidant. LOEW describes additional details regarding the components of a Ginkgo extract, and CARINI discloses that Ginkgo-phosphatidylcholine has

cardioprotective activity and increases plasma antioxidant capacity. Based essentially on the same rationale stated above, the combination of SUMMERS, LOEW and CARINI fails to teach or suggest that a ginkgo-phospatidylserine complex could have the specific effects, i.e, improving the speed of memory and memory quality, counteracting cognitive fatigue in normal healthy persons, or preventing the deterioration of the speed of memory in people with decreased cognitive function, as specified in claim 35.

For all of the reasons set forth above, SUMMER, LOEW and CARINI fail to teach or suggest, and fail to render obvious, the method of claim 35. Accordingly, this aspect of the rejection cannot be maintained.

C. Claims 36-42

The references fail to teach or suggest a Ginkgo-phosphatidylserine complex for treating a disease related to the reduction of cognitive function and mental fatigue.

As detailed in the above remarks, SUMMERS discloses a supplement combination of a phosphoester and an antioxidant. LOEW describes additional details regarding the components of a Ginkgo extract, and CARINI discloses that Ginkgo-phosphatidylcholine has cardioprotective activity and increases plasma antioxidant capacity. Based essentially on the same rationale stated above, the combination of SUMMERS, LOEW and CARINI fails to teach or suggest that a ginkgo-phospatidylserine complex could be used to

treat a disease related to the reduction of cognitive function and mental fatigue, such as Dementia and Alzheimer's disease.

For all of the reasons set forth above, SUMMER, LOEW and CARINI fail to teach or suggest, and fail to render obvious, the method of claims 36-42. Accordingly, this aspect of the rejection cannot be maintained.

D. Conclusion

In view of the foregoing, it follows that the rejection of claims 23-42 and 46 under 35 U.S.C. § 103(a) as being unpatentable over SUMMER, LOEW and CARINI is improper and should be reversed. Accordingly, Applicants respectfully request reversal of the rejections.

The Appeal Brief fee of $540.00 is being paid online simultaneously herewith by credit card.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any underpayment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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Enclosures: Claims Appendix

(8) Claims Appendix

23. A method for the enhancement of cognitive function and alleviation of mental fatigue, said method comprising: administering, to a subject in need thereof, *Ginkgo* complexed with a phospholipid containing 10 to 50% of phosphatidylserine.

24. The method according to claim 23, wherein the phospholipid contains from 20 to 40% of phosphatidylserine.

25. The method according to claim 23, wherein the phospholipid contains 20% of phosphatidylserine.

26. The method according to claim 23, wherein the *Ginkgo* is derived from the plant *Ginkgo biloba*, extracts thereof and/or one or more principal active substances thereof.

27. The method according to claim 26, wherein one of the principal active substances is bilobalide.

28. The method according to claim 26, wherein the *Ginkgo* extract contains at least about 20% *Ginkgo* flavone glycosides and about 2 to about 10% terpene lactones.

29. The method according to claim 23, wherein the ratio between *Ginkgo* and the phosphatidylserine in the complex is about 1:3.

30. The method according to claim 23, wherein the Ginkgo phospholipid complex is in a medicament or a dietary supplement that is administered in the form of tablets, granules, powders, capsules, syrups, solutions, suspensions, dragees, gels, injections or drops.

31. The method according to claim 23, wherein the Ginkgo phospholipid complex is in a medicament or a dietary supplement and is formulated for oral administration.

32. The method according to claim 23, wherein the *Ginkgo* phosphatidylserine complex is in a medicament or a dietary supplement that is administered in an amount of about 20 to about 240 mg per day, or in an amount of about 60 to about 120 mg per day.

33. The method according to claim 23, wherein the Ginkgo phospholipid complex is in a medicament or a dietary supplement, and further contains a pharmaceutically acceptable amount of at least one additive selected from the group consisting of minerals, vitamins, sweeteners, flavors,

pharmaceutically acceptable carriers, auxiliary and binder agents, excipients and mixtures thereof.

34. The method according to claim 33, wherein the additive is selected from vitamins, minerals and mixtures thereof, and/or is selected from calcium, fluorine, phosphorus, copper, potassium, manganese, magnesium selenium, zinc and iron, Vitamin A, Vitamins B1, B2 and B12, Vitamin C, Vitamin D2, nicotinamide, calcium pantotenate, rutoside and Vitamin E.

35. A method for the enhancement of cognitive function and alleviation of mental fatigue by improving the speed of memory and memory quality, by counteracting cognitive fatigue in normal, healthy persons or by preventing deterioration of the speed of memory in people with decreased cognitive functions, said method comprising administering, to a subject in need thereof, an effective amount of a *Ginkgo* complexed with phosphatidylserine.

36. A method for the treatment and prevention of a disease related with the reduction of cognitive function and mental fatigue, said method comprising administering, to a subject in need thereof, an effective amount of a *Ginkgo* complexed with phosphatidylserine.

37. The method according to claim 36, wherein the disease is Dementia.

38. The method according to claim 37, wherein the disease is Alzheimer's Disease.

39. The method according to claim 36, wherein the *Ginkgo* phosphatidylserine complex is in a medicament or a dietary supplement, and further contains a pharmaceutically acceptable amount of at least one additive selected from the group consisting of vitamins, minerals, sweeteners, flavors, pharmaceutically acceptable carriers, auxiliary and binder agents, excipients and mixtures thereof.

40. The method according to claim 36, further comprising administering a pharmaceutical compound used for the treatment and prevention of the disease to be treated related with the reduction of cognitive function and mental fatigue.

41. The method according to claim 40, wherein the pharmaceutical compound is an acetylcholinesterase inhibitor.

42. The method according to claim 40, further comprising administering complexed grape seed extract, as an additionally active compound.

46. The method of claim 23, wherein the ratio between Ginkgo and the phosphatidylserine is 0.5-1:2-5.

(9) Evidence Appendix

None.

(10) Related Proceedings Appendix

None.